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Update on RG6042 (formerly known as IONIS-HTT$_{Rx}$) Huntington's disease global development programme: Two clinical studies to begin by end of 2018

Dear Global Huntington's Community,

Thank you for your ongoing support and interest in the investigational medicine RG6042 for Huntington's disease (HD).

Over the past months we and our partner Ionis Pharmaceuticals have been heavily engaged with communities around the world (patient groups, medical professionals, Health Authorities and payers) to collaborate and build the RG6042 global development programme and upcoming studies. We are eager for RG6042 to advance into further clinical development. In addition, as announced last month, the European Medicines Agency granted RG6042 PRIME ("PRIority MEdicine") designation, which provides promising medicines enhanced interactions with the agency and the potential for accelerated evaluation.

Next steps for the global RG6042 development programme
Following the completion of the Phase I/IIa first-in-human study of RG6042 in December, there are several important questions that still need to be answered before this investigational medicine can potentially be approved by Health Authorities in countries around the world:

- What are the effects on lowering mutant huntingtin (mHTT), the toxic protein believed to cause HD, over a period of time longer than the 13-week Phase I/IIa study?
- Does sustained treatment with RG6042 slow or stop the progression of HD?
- Do any safety concerns emerge when RG6042 is given to a larger group of people, and for a longer time, than the 46 individuals in the Phase I/IIa?
- Could a less frequent dose than the monthly dose used in the Phase I/IIa study be effective?

Our upcoming studies have been designed to answer these questions as quickly and as robustly as possible, whilst considering the number of people exposed to an investigational medicine or placebo.

Update on ongoing and upcoming clinical studies
All 46 participants who took part in the Phase I/IIa study are continuing to receive RG6042 as part of an 'open-label extension' study run by Ionis. This study assesses the safety and tolerability of longer-term dosing of RG6042 and is being conducted at the nine sites involved in the Phase I/IIa study in Canada, Germany and the United Kingdom.

Two additional clinical studies, run by Roche, are planned to start by the end of 2018. Information about these studies was presented today to the HD community during the European Huntington's Disease Network Plenary Meeting in Vienna, Austria.

- **The HD Natural History Study:** This 15-month observational study aims to further understand the role of mHTT in disease progression. There is no drug treatment in this study, as the goal is to understand the natural progression of HD. This study will include up to 100 participants with early manifest (Stage I and II) HD at up to 17 sites in Canada, Germany, the United Kingdom and the United States. This study is expected to start towards the end of 2018.
- **GENERATION HD1:** This will be the world's first Phase III study testing a molecule designed to lower huntingtin protein. The study design will be submitted to Health Authorities and Ethics Committees/Institutional Review Boards (IRBs) this year. The GENERATION HD1 study will

evaluate the efficacy and safety of RG6042 treatment given once per month or once every two months (bi-monthly) over a period of 25 months (approx. two years).
  - This global study will enrol up to 660 patients with manifest HD at 80-90 sites in approximately 15 countries around the world. The study is expected to begin at the end of 2018 with patients starting to enrol by early 2019.
  - Participants will be randomised to one of three treatment study arms: RG6042 monthly, RG6042 bi-monthly or placebo monthly. This means for every two participants randomised to RG6042, one will receive placebo. The study is designed to test the potential effects of RG6042 compared to placebo, whilst limiting the number of people who will be given placebo.
  - The study is "double-blinded," meaning neither the participant nor his/her investigator or site staff will know which study arm the participant is assigned.
- **Future open-label extension study for all patients who complete the HD Natural History and GENERATION HD1 studies:** If approved by Authorities and Ethics Committees/IRBs, and if data support the continued development of RG6042, we plan to offer an open-label extension study that would provide the option of receiving RG6042 (no placebo control) to all patients who complete these studies.

Our team is working with urgency to start the HD Natural History and GENERATION HD1 studies and we understand that you are eager for more detailed information, such as specific sites, countries and dates.

Study site/country information will be shared on a progressive basis. Once a site is nearly ready to enrol patients, we will update the information on clinicaltrials.gov and on North America's HDTrialFinder.org. On the next pages of this letter you'll find additional study information and frequently asked questions and answers about these new studies.

The urgency in which families are seeking a medicine that can slow or stop the progression of HD is deeply felt and shared by our team. Because the need in HD is greater than the capacity of our development programme, we recognise that not every person, nor every capable HD clinic or centre, interested in participating in these clinical studies will be able to participate. Please understand the studies are designed to provide Authorities with the required data so that the benefit-risk of RG6042 can be determined as quickly as possible.

Our team is committed to addressing the scientific questions and promptly completing the RG6042 studies with appropriate rigour. The ultimate goal is that this investigational medicine can be approved by Health Authorities, and made accessible to the broader HD community – a goal that we share with you, the global HD community.

We look forward to providing you updates later this year, and we thank you for your continued partnership.

Sincerely,

Mai-Lise Nguyen, on behalf of the Roche HD team
Patient Partnership Director, Rare Diseases
Roche Pharma Research & Early Development / Roche Innovation Centre Basel, Switzerland

Below is an overview about the upcoming studies. Further details about the studies will be posted on clinicaltrials.gov and on North America's HDTrialFinder.org as information is finalised.

	HD Natural History Study	**GENERATION HD1 Study**
Objective	Observational study to further understand the role of mHTT in disease progression in early manifest HD	Global Phase III efficacy and safety study evaluating RG6042 in broader manifest HD
Study status	Expected to begin towards the end of 2018	Expected to begin at the end of 2018 with patients starting to enrol by early 2019, pending approval by Health Authorities and Ethics Committees/IRBs
Number of patients	Up to 100 individuals with early manifest HD between the ages of 25-65	Up to 660 individuals with manifest HD between the ages of 25-65
Number of sites	Up to 17 sites in Canada, Germany, the United Kingdom and the United States *Sites will be announced on a progressive basis, once each site is nearly ready to enrol participants*	80-90 sites in approximately 15 countries around the world *Countries/sites will be announced on a progressive basis, once each are nearly ready to enrol participants*
General study information and participant commitment	● Participants will not receive any drug treatment in this observational study, because the goal is to understand the natural progression of HD and changes in mHTT levels ● Participants will be monitored over 15 months with procedures including lumbar puncture (4 times over the course of the study), MRI scans, blood tests, neurological examinations, and the use of digital monitoring technologies ● A 'study companion' is encouraged (but not required) to also participate with the patient – to provide support and contribute to data collection	● Study participation will include a 25-month treatment period (approx. 2 years) plus follow-up ● Participants will be randomised to one of three study arms o 220 participants will receive RG6042 once per month o 220 participants will receive RG6042 once every two months, and a placebo on the off months o 220 participants will receive a placebo once per month ● The study is "double-blinded," meaning neither the participant nor his/her investigator or site staff will know which study arm the participant is assigned ● Regardless of study arm, all participants will undergo monthly procedures, including a lumbar puncture injection, so that study integrity is maintained ● A 'study companion' is encouraged (but not required) to also participate with the patient – to provide support and contribute to data collection

Frequently asked questions and answers

What happens next?
Our team is working with urgency to complete setup of the upcoming clinical studies. This includes obtaining appropriate approvals (from Health Authorities and Ethics Committees/IRBs for each site), training sites, providing materials and resources for study procedures, and importantly ensuring high quality and supply of study drug. We will continue to provide updates as the setup process continues for the HD Natural History and GENERATION HD1 studies. Details about the studies will be posted on clinicaltrials.gov and on North America's HDTrialFinder.org as information is finalised.

What does "early manifest HD" and "manifest HD" mean?
Someone with early manifest HD is described as someone for which motor (movement) symptoms have presented, but the person is living at home, is able to take care of him/herself and is generally able to work; this is described as Stage I/II HD, according to the Total Functional Capacity (TFC) Scale, a commonly used clinical measure in HD research.

Manifest HD is a broader term, which also includes moderate to some more advanced stages of HD. These individuals are able to live at home, but may also have minor difficulties with activities of daily living; this generally corresponds to Stages I, II and some of Stage III, according to the TFC Scale.

How can I tell if I am/a loved one is eligible for participation in one of the clinical studies?
The observational HD Natural History Study will enrol people with early manifest HD between the ages of 25-65, and who fulfil additional eligibility criteria. The planned Phase III GENERATION HD1 study will enrol people with manifest HD between the ages of 25-65, and who fulfil additional eligibility criteria. Individuals interested in the GENERATION HD1 study should also feel capable of undertaking a comprehensive, 25-months long study and have the support of his/her HD specialist and site investigator. Further details of studies, including inclusion and exclusion criteria, will be posted on clinicaltrials.gov and on North America's HDTrialFinder.org, as well as shared with HD healthcare professionals.

We encourage you to speak to your/your loved one's HD specialist about what may be best for your situation. Your HD specialist can also contact Roche Medical Information in your local country for more information.

Why are you doing an observational natural history study?
The HD Natural History study will further the understanding of the role of mHTT in natural disease progression, including how levels of mHTT change over time in the absence of any drug treatment. This study will enrol patients with a similar profile, e.g., CAG repeat length and age, as those who are participating in the ongoing open-label extension study.

How are the clinical study sites selected?
A variety of factors influence site selection, including assessments on experience with HD studies, clinic infrastructure capacity to run the study as well as usual site activities, ability to operationalise the study as quickly and completely as possible, patient population, and geographic location.

Whether your HD clinic or centre is selected for participation or not, this is no reflection on the quality of the many outstanding HD clinics and dedicated care providers around the world. The need in HD is greater than the capacity of our development programme. We have designed the programme to provide the required data to Authorities so that the benefit-risk of RG6042 can be determined as quickly as possible. Our ultimate goal is that this investigational medicine can be approved by Health Authorities, and made accessible to the broader HD community.

Can you provide a list of expected clinical study sites?
Study sites will be announced on a progressive basis – for example, once a site's infrastructure and approvals (from Health Authorities and Ethics Committees/IRBs) are in place, and sites are nearly ready to enrol patients. For any clinical study, it is possible that an expected study site does not

proceed to enrol participants. This can be for various reasons and we do not want to raise hopes or expectations.

What if there is not a study site near where I live? Can I relocate to participate in a study?
Clinical studies are subject to international, national and local laws and regulations. Additionally, factors such as institutional site policies, health insurance and travel burden may impact your ability to relocate and be accepted into one of the study sites. Eligibility and enrolment are decided by the study investigator at each site, who takes into account all these factors and may also wish to speak to you or your local HD specialist for more information.

Whether your HD clinic or centre is selected for participation or not, this is no reflection on the quality of the many outstanding HD clinics and dedicated care providers around the world. The need in HD is greater than the capacity of our development programme. We have designed the programme to provide the required data to Authorities so that the benefit-risk of RG6042 can be determined as quickly as possible. Our ultimate goal is that this investigational medicine can be approved by Health Authorities, and made accessible to the broader HD community.

Can I access RG6042 outside of clinical studies?
At this time, access to RG6042 is only through clinical study participation because the benefits and risks of RG6042 are not yet fully understood. This means that we are not able to grant pre-approval, compassionate use or "right-to-try" requests at this time. As our understanding of the benefits and risks of RG6042 grows, we will regularly evaluate this position.

Your clinical studies are in early manifest and manifest HD. Will you study RG6042 in other patient populations (e.g., juvenile onset HD, pre-manifest or prodromal HD)?
We recognise the critical medical need for a treatment for HD, especially for people living with severe forms like juvenile onset HD. In consultation with HD community experts, our team will explore the potential use of RG6042 in populations beyond manifest HD once there is sufficient scientific and safety rationale.

For the Phase III GENERATION HD1 study, how are you ensuring scientific rigour?
Pending approval by Health Authorities and Ethics Committees/IRBs, the GENERATION HD1 study will be a multi-centre, randomised, double-blind, placebo-controlled study, which is considered a "gold-standard" research approach to avoid biased study results. These terms mean:

- Multi-centre: The study will occur at multiple sites with different investigators and staff
- Randomised: The process by which study drug (active or placebo) will be assigned to participants is by chance (random), and not by choice. Based on study design, for every two participants randomised to RG6042, one will receive placebo.
- Double-blind: Neither the participant nor his/her investigator or site staff will know which study arm (treatment or placebo) the participant is assigned
- Placebo-controlled: The investigational medicine, in this case RG6042, will be compared against the use of a placebo

What is the placebo in GENERATION HD1, and why is it being used?
The placebo that will be used in the planned GENERATION HD1 study is an inactive substance. The placebo will look like RG6042 (a clear liquid) and will be injected into the body using the same intrathecal (lumbar puncture) procedure, but it is not active drug.

As we enter the final phase of clinical development with a global Phase III study in manifest HD, it is important to determine if potential effects or safety concerns observed in the study are due to RG6042 treatment - and not to other effects (for example, expectations of anyone involved with the clinical study). This information is critical to provide to Authorities to help them determine the benefit-risk of treatment with RG6042.